

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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27 NOV 2000 PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT  
(PCT Rule 71.1)

Date of mailing  
(day/month/year) 24.11.2000

Applicant's or agent's file reference  
PS/P21178WO

## IMPORTANT NOTIFICATION

International application No.  
PCT/EP99/07719

International filing date (day/month/year)  
10/09/1999

Priority date (day/month/year)  
10/09/1998

Applicant  
ERASMUS UNIVERSITEIT ROTTERDAM et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

#### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>PS/P21178WO</b>	<div style="display: flex; justify-content: space-between;"> <div> <b>FOR FURTHER ACTION</b> </div> <div>           See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)         </div> </div>	
International application No. <b>PCT/EP99/07719</b>	International filing date (day/month/year) <b>10/09/1999</b>	Priority date (day/month/year) <b>10/09/1998</b>
International Patent Classification (IPC) or national classification and IPC <b>C12Q1/68</b>		
Applicant <b>ERASMUS UNIVERSITEIT ROTTERDAM et al.</b>		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 3 sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I <input checked="" type="checkbox"/> Basis of the report</li> <li>II <input type="checkbox"/> Priority</li> <li>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV <input type="checkbox"/> Lack of unity of invention</li> <li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI <input type="checkbox"/> Certain documents cited</li> <li>VII <input checked="" type="checkbox"/> Certain defects in the international application</li> <li>VIII <input checked="" type="checkbox"/> Certain observations on the international application</li> </ul>		
Date of submission of the demand  <b>04/04/2000</b>	Date of completion of this report  <b>24.11.2000</b>	
Name and mailing address of the international preliminary examining authority:  <div style="display: flex; align-items: center;"> <div>             European Patent Office              D-80298 Munich              Tel. +49 89 2399 - 0 Tx: 523656 epmu d              Fax: +49 89 2399 - 4465           </div> </div>	Authorized officer  <b>Jacques, P</b>  Telephone No. +49 89 2399 8934	



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/07719

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).*):

### Description, pages:

1-22 as originally filed

### Claims, No.:

1-26 as received on 17/10/2000 with letter of 16/10/2000

### Drawings, sheets:

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

**see separate sheet**

6. Additional observations, if necessary:

### III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-10, 13-21.

because:

☒ the said international application, or the said claims Nos. 1-10, 13-17, 21 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☒ the claims, or said claims Nos. 18-21 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

### V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

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International application No. PCT/EP99/07719

Novelty (N)	Yes:	Claims	1-17, 22-26
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-17, 22-26
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	11-12, 22-26
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

## VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**Re Item I**

**Basis of the report**

1. The amendments filed introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(b) PCT. The amendments concerned are the following: "or any other technique suitable for determining the genotype of a subject" in claim 5.

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. Claims 1-10, 13-17 and 21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).  
In this context, claims 1-10 are considered to fall under the concept of an "in vivo" method of diagnosis and claims 13-17 and 21 are considered to fall under the concept of a method of treatment.
2. The subject-matter of claims 18 to 21 is so unclear that it appears meaningless to assess novelty, inventive step and industrial applicability (see point 1 under Item VIII).

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Reference is made to the following document/:

D1: UITTERLINDEN ET AL.: 'VITAMIN D RECEPTOR GENOTYPE IS ASSOCIATED WITH RADIOGRAPHIC OSTEOARTHRITIS AT THE KNEE' J. CLIN. INVEST., vol. 100, no. 2, 1997, pages 259-263.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/EP99/07719

2. As the particular combination of features of independent claim 1 is not disclosed in any cited prior art, the subject-matter of the said claim would appear to be novel (Article 33(2) PCT).

3. Moreover, the subject-matter of claim 1 appears to involve an inventive step in the sense of Article 33(3) PCT for the following reasons:

The closest state of the art is considered to result from document D1.

This document describes the association between vitamin D receptor genotype and osteoarthritis. More particularly, the said document discloses that the baT haplotype of the vitamin D receptor gene is associated with a 2.27 increased risk of radiographic osteoarthritis (page 260, column 2).

The subject-matter of claim 1 is distinguished therefrom by the following feature: the baT haplotype of the vitamin D receptor gene is associated with risk of bone fracture. The technical effect of this distinguishing feature result in the determination of the susceptibility of a subject to bone fracture.

The technical problem to be solved by the invention was therefore to provide a method of determining susceptibility to bone fracture in a subject.

The problem posed has convincingly been solved by the identification of the relationship between the baT haplotype of the vitamin D receptor gene and bone fracture.

As no specific instructions or indications to identify the said relationship can be found in the cited prior art, the subject-matter of claim 1 can be considered to involve an inventive step in the sense of Article 33(3) PCT.

The same applies to dependent claims 2 to 17.

4. The subject-matter of claim 22 relates to the use of a kit to determine susceptibility to bone fracture. As the said use being equivalent to the method disclosed in claim 1, the same reasoning as for the said claim applies to claim 22 (see above points 2 and 3) which is new (Article 33(2) PCT) and involves an inventive step (Article 33(3) PCT).

The same applies to dependent claim 23.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/EP99/07719

5. The subject-matter of claim 24 being a kit to perform the method disclosed in claim 1, the same reasoning as for the said claim applies to claim 24 which is new (Article 33(2) PCT and involves an inventive step (Article 33(3) PCT).

The same applies to dependent claim 25 and 26.

6. For the assessment of the present claims 1-10, 13-17 and 21 on the question whether they are industrially applicable, no unified criteria exist in the PCT. Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VII**

**Certain defects in the international application**

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.

**Re Item VIII**

**Certain observations on the international application**

1. The subject-matter of claim 18 does not meet the requirements of Article 5 and 6 PCT for the following reasons:

The subject-matter of the said claim is a method of predicting response of a subject to treatment, said method comprising analysing the genetic material of a subject to determine the presence of the baT haplotype of the vitamin D receptor gene, wherein said haplotype is associated with risk of bone fracture.

Firstly, it is not clear to which treatment the said claim is directed.

Moreover, the description states that the presence of the baT haplotype is associated



with risk of bone fracture, the said risk being independent of bone mineral density in a subject (page 4, lines 20-24). However, the mechanisms underlying the increase risk in bone fracture are not explained. Furthermore, document D1 discloses that the same baT haplotype of the vitamine D receptor gene is also associated with osteoarthritis (page 260, column 2), a different disease. Thus, the skilled man would not be able to predict the response of a subject, presenting the baT haplotype, to a particular treatment among those available (e.g. anabolic steroids, biphosphonate, vitamin D preparations, calcium supplements, hormone replacement therapy).

In addition, the description on page 10, line 25 states that the effect of a therapeutic or preventive agent may depend on the underlying cause of heart disease. The effect of the said disease on the predictive response of a subject to treatment is not at all clear.

As the subject-matter of claim 18 (and dependent claims 19, 20 and 21) is not convincingly supported by the description which would give sufficient guidance to a person skilled in the art to apply the claimed method, it does not satisfy to the requirements of both Articles 5 and 6 PCT.

2. The subject-matter of claim 2 is not clear (Article 6 PCT) as the said claim relates to a method of determining susceptibility to bone damage, whereas claim 1, to which it is dependent, is directed to a method of determining susceptibility to bone fracture. Such verbal inconsistency introduces a lack of clarity (Article 6 PCT).

# INTERNATIONAL SEARCH REPORT

International Application No.  
**PCT/EP 99/07719**

**A. CLASSIFICATION OF SUBJECT MATTER**  
**IPC 7 C12Q1/68**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
**IPC 7 C12Q**

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RALSTON : "THE GENETICS OF OSTEOPOROSIS" Q J MED, vol. 90, 1997, pages 247-251, XP000870120 the whole document	1-25
X	RALSTON: "GENETIC MARKERS OF BONE METABOLISM AND BONE DISEASE" SCAND J CLIN LAB INVEST, vol. 57, Suppl. 227, 1997, pages 114-121, XP000867324 the whole document	1-25
X	WO 94 03633 A (GARVAN INST MED RES ;MORRISON NIGEL ALEXANDER (AU); EISMAN JOHN AL) 17 February 1994 (1994-02-17)	1-3
Y	the whole document	4-25
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"S" document member of the same patent family

Date of the actual completion of the international search

**14 February 2000**

Date of mailing of the international search report

**28/02/2000**

Name and mailing address of the ISA

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**Hagenmaier, S**

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/ 07719

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 15-19, 22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/07719

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 40187 A (GEMINI INTERNATIONAL HOLDINGS ;SPECTOR TIMOTHY DAVID (GB); KEEN RI) 30 October 1997 (1997-10-30)	1-3
Y	the whole document	4-25
X	UITTERLINDEN ET AL.: "VITAMIN D RECEPTOR GENOTYPE IS ASSOCIATED WITH RADIOGRAPHIC OSTEOARTHRITIS AT THE KNEE" J. CLIN. INVEST., vol. 100, no. 2, 1997, pages 259-263, XP002130404	1-3
Y	the whole document	4-25
X	UITTERLINDEN ET AL.: "A LARGE SCALE POPULATION-BASED STUDY OF THE ASSOCIATION OF VITAMIN D RECEPTOR GENE POLYMORPHISMS WITH BONE MINERAL DENSITY" J. BONE AND MINERAL RESEARCH, vol. 11, no. 9, 1996, pages 1241-1248, XP000874270	1-3
Y	cited in the application the whole document	4-25
Y	UITTERLINDEN ET AL.: "RELATION OF ALLELES OF THE COLLAGEN TYPE I ALPHA1 GENE TO BONE DENSITY AND THE RISK OF OSTEOPOROTIC FRACTURES IN POSTMENOPAUSAL WOMEN" NEW ENGL J MED, vol. 338, 9 April 1998 (1998-04-09), pages 1016-1021, XP000876678	4-25
	cited in the application the whole document	
Y	GRANT ET AL.: "REDUCED BONE DENSITY AND OSTEOPOROSIS ASSOCIATED WITH A POLYMORPHIC Sp1 BINDING SITE IN THE COLLAGEN TYPE I ALPHA 1 GENE" NATURE GENETICS, vol. 14, 1996, pages 203-205, XP000867512	4-25
	cited in the application the whole document	
Y	UITTERLINDEN ET AL.: "SP1 BINDING SITE POLYMORPHISM IN THE COLA1 GENE IS ASSOCIATED WITH BMD: THE ROTTERDAM STUDY" OSTEOPOROSIS INTERNATIONAL, vol. 6 SUPPL.1, 1996, page 124, PSu164 XP000874224	4-25
	the whole document	

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/07719

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
W0 9403633 A	17-02-1994	AU 673187 B	31-10-1996
		AU 4690093 A	03-03-1994
		CA 2141300 A	17-02-1994
		EP 0652975 A	17-05-1995
		JP 8501933 T	05-03-1996
		US 5593833 A	14-01-1997
W0 9740187 A	30-10-1997	AU 2395697 A	12-11-1997
		CA 2251744 A	30-10-1997
		EP 0909330 A	21-04-1999
		US 5939260 A	17-08-1999